California MEDICINE

OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION

VOL. 70 MAY 1949 No. 5

Blood Transfusions and the Rh Factor

PAUL G. HATTERSLEY, M.D., *San Francisco*

SUMMARY

When Rh-negative persons are given transfusions of Rh-positive blood, more than 50 per cent are sensitized to the Rh_0 factor. Such sensitization of female children may be the cause of hemolytic disease in their offspring many years later, while severe hemolytic reactions may follow a second transfusion of Rh-positive blood in either sex.

The gross hemolysis of transfused blood may be entirely asymptomatic, however. In one case a pint of blood was completely hemolyzed within two hours without producing symptoms. The only signs were hemoglobinuria, low grade jaundice, urobilinogenuria and a rising Rh antibody titer. The patient had previously been sensitized by a single pint of Rh-positive blood.

The dangers of Rh sensitization can be avoided by routine Rh typing of all prospective recipients of transfusion, whether male or female, and by giving only Rh-negative blood to those who are Rh-negative.

SINCE 1940, when Landsteiner and Wiener[5] first described the newly discovered "Rhesus factor" in human erythrocytes, certain basic facts regarding this factor have become so well established and so generally known as to require only the briefest review:

1. The Rh and Hr factors are a group of antigenic substances which occur in various combinations in the red blood cells of all human beings.

2. These factors are hereditary characteristics determined by corresponding genes, each factor being a simple mendelian characteristic, dominant over its absence.

3. The Rh factors, being antigenic substances, are capable of stimulating the production of type-specific antibodies when cells containing these antigens are injected into receptive individuals or into suitable experimental animals. Antibodies corresponding to each of the known Rh and Hr antigens have been found in the blood of sensitized patients. Sera containing these antibodies are utilized in typing human erythrocytes.

4. A single member of this group of antigens, the Rh_0 (or D of Fisher) has proven by far the most important, probably 99 per cent of all Rh sensitizations occurring among the 15 per cent of persons whose cells lack this antigen. Because of this fact, the anti-Rh_0 (anti-D) serum is known as the routine or diagnostic Rh-typing serum, and patients are classified as Rh-positive or Rh-negative on the basis of the reaction of their cells in this serum.

5. Sensitization of Rh-negative patients to the Rh factors occurs in two ways: First, by transfusion with Rh-positive blood; and, second, by repeated pregnancy and delivery of Rh-positive infants. In the latter case, the fetus receives the dominant Rh-positive gene from the Rh-positive father. It is probable that during the latter months of pregnancy, when the placental villi become progressively thinner, with less of a barrier separating fetal and maternal circulations, some fetal red blood cells, containing the Rh antigen, pass into the maternal circulation, where they stimulate the formation

From the Department of Medicine, Stanford University School of Medicine, San Francisco.

Read as a part of a Symposium on Hematology before a joint meeting of the Sections on General Medicine and Public Health at the 77th Annual Session of the California Medical Association in San Francisco, April 11-14, 1948.

of Rh antibodies. These antibodies in turn diffuse back into the fetal blood, where they destroy the fetal red blood cells and tissues, causing the disease known as erythroblastosis fetalis, or hemolytic disease of the newborn.

These are the general facts concerning Rh, facts which concern primarily the obstetrician, the pediatrician and the clinical pathologist. There is one aspect of the subject, however, with which every practicing physician should be acquainted, in this day of increasing use of blood transfusions. I refer to the serious hazard of sensitization of the Rh-negative patient by transfusion.

It has been estimated that from 1 in 25 to 1 in 50[9, 11] Rh-negative women who give birth to Rh-positive infants become sensitized to the Rh factor. It was for some time considered that the remainder were incapable of producing Rh antibodies, and that the incidence of sensitization by transfusion was very similar to that by pregnancy.

Some relatively recent work, however, has demonstrated that the *majority* of Rh-negative persons develop Rh antibodies following repeated transfusions of Rh-positive blood. Diamond and his coworkers[1, 2] studied a group of several hundred Rh-negative service men who had received blood transfusions overseas, and found that over 50 per cent of them had demonstrable Rh antibodies in their sera. These observations have been corroborated in smaller series elsewhere.[4, 8] Diamond[1] likewise found Rh antibodies in the sera of a majority of unmarried Rh-negative women who had received blood transfusions; and among a small series of women who had experienced both transfusions and pregnancies, nearly all showed evidence of sensitization. More recently Diamond[5] and Wiener and Sonn-Gordon[12] succeeded in sensitizing a very large percentage of Rh-negative volunteers by repeated injections of Rh-positive blood.

That sensitization by transfusion may be responsible for severe hemolytic disease in infants born to such women has, of course, been well established. The following is a characteristic case:

CASE REPORT

A 25-year-old housewife was referred because of the death of her first two infants. The first was born at term and appeared normal, but rapidly developed intense jaundice and died on the second day. The second pregnancy, two years later, resulted in a stillborn hydropic fetus. Pathologic examinations on both infants revealed the characteristic picture of severe erythroblastosis fetalis.

Laboratory tests showed the patient's blood to be group A, Rh-negative, and the serum contained hyperimmune antibodies of Rh_0 specificity to a titer of 512. Her husband was Rh-positive, type Rh_1, Hr'-negative and Hr_0-negative (CDe/CDe). As these reactions indicated that he was homozygous Rh-positive, and that any children he might have would likewise be Rh-positive, it was necessary to advise this young couple that their chance for having children of their own was extremely poor.

Careful history revealed that as a girl, this patient had received a series of transfusions for anemia associated with nephritis.

Cases of this sort are unfortunately not particularly rare. Levine and Waller[6] have reported a series of 19, some of the patients having been sensitized by transfusion in early childhood. There is much evidence that Rh sensitization, once it is gained, is never lost. Even though the antibody may disappear from the blood, subsequent exposure to the Rh antigen elicits its prompt reappearance.

It is also rather common to encounter women who have had one or more perfectly normal children, but who then, following a transfusion, have delivered severely affected infants. It is becoming increasingly recognized that in order to prevent such tragedies, the Rh-negative female who has not passed childbearing age should never receive transfusions of Rh-positive blood—even in infancy.

On the other hand it is certainly less generally realized that even among male patients transfusion without preliminary Rh typing may be very dangerous. The picture of the acute transfusion reaction in its classic form is all too well known: The sudden chill with substernal or lumbar pain, the fall in blood pressure, often to shock levels, and the subsequent urinary suppression and uremia, often terminating fatally. Such reactions are fortunately rather rare, usually following transfusion with blood of incompatible major blood group. The fact that transfusion reactions due to Rh incompatibility are only rather rarely reported, and are usually among postpartum women, has been responsible for the common belief that Rh sensitization by transfusion is an unusual occurrence, and that it is only among the female population that routine Rh typing before transfusion should be practiced.

It has been pointed out by various workers,[3, 7] however, that hemolysis of transfused cells may occur without the characteristic signs and symptoms. It has been suggested that the lack of symptoms is due to the fact that the transfused cells are hemolyzed slowly in such cases, rather than immediately, as they presumably are when, for instance, group A blood is given to a group O patient. That asymptomatic hemolytic reactions do occur, but that even in such cases destruction of the hemolyzed blood may be very rapid, is illustrated by the following case:

CASE REPORT

A 48-year-old male Army officer received his first transfusion when injured in the Philippines. Six months later he was brought to a San Francisco hospital for surgical repair of his injuries, and while in the operating room he received 500 cc. of two-day-old whole bank blood drawn into acid citrate dextrose solution. Due to a clerical error in the laboratory, this patient had been recorded as Rh-positive, although he actually had not been Rh-typed at all. His blood was cross-matched with that of a group A Rh-positive donor, saline-suspended cells of patient and donor each being incubated with the serum of the other for 30 minutes at 37° C., and the tubes centrifuged. Since the cross-match showed no agglutination, the blood was considered compatible, and was sent to the operating room. The patient, who was conscious throughout the transfusion, did not complain of chill or discomfort, the blood pressure remained steady, and during the subsequent hours there was no elevation of temperature.

In the meantime the error had been discovered, and it was determined that the patient was actually Rh-negative. Another blood specimen was drawn immediately after his return from the operating room, and the Rh typing confirmed. In examining this specimen, however, two unexpected discoveries were made: (1) The patient's serum was brownish and appeared to contain not only an increase in bilirubin, but free hemoglobin as well; (2) although it had been less than two hours since he had received a pint of Rh-positive blood, *no Rh-positive cells could be found in the specimen.** It appeared that the transfused cells had been completely hemolyzed. The pre-transfusion blood specimen that had been taken from the patient then was tested for Rh antibodies, and was found to have hyperimmune antibodies of Rh_0 specificity to a titer of 64, and of Rh′ specificity to a titer of 8. There was no activity in saline.

During the ensuing 24 hours the patient passed brownish urine which gave a positive reaction to a chemical test for hemoglobin and which contained large amounts of urobilinogen. Although there was only the faintest discernible trace of icterus of the sclerae, the serum bilirubin rose to 3.0 mg. per 100 cc., the one-minute test being negative. Hemoglobinuria and bilirubinemia soon cleared, there was no suppression of urinary output, and during the three months that the patient was followed at this hospital, blood urea did not rise above normal levels. At the end of that time the only demonstrable effect of the transfusion reaction was his Rh-antibody titer which had risen to 4,000.

There are several lessons to be learned from this case, other than the obvious importance of keeping clerical errors out of the transfusion section: (1) The patient had been sensitized by a single transfusion six months before. Although sensitization is usually said to occur only after several transfusions, the author not infrequently has noted antibodies in the serum of patients who have received only one or two transfusions and who could not have been sensitized by pregnancy. (2) Although the patient's serum contained definite Rh antibodies, the routine tube cross-match with the Rh-positive bank blood did not reveal the incompatibility. This was due to the fact that the cross-match technique, although one widely used, was not designed to detect the *hyperimmune* or *blocking* type of Rh antibodies which usually occur in the blood of individuals sensitized by transfusions and which do not agglutinate saline-suspended cells. (3) Although the erythrocytes of an entire pint of blood apparently were hemolyzed within two hours, there were none of the symptoms usually associated with acute hemolytic reactions, and the only signs—the hemoglobinuria and icterus—were so minimal as to be missed entirely by the clinician until pointed out to him by a member of the transfusion section.

There is much reason to believe that asymptomatic transfusion reactions of this sort are not uncommon. Although the practice at Stanford University Hospital of routinely Rh-typing the blood of all patients who are to be given transfusion has obviated such reactions, the author has observed a few patients at other hospitals who hemolyzed one or more pints of blood with little or nothing in the way of symptoms. Likewise the author has seen a number of patients who had received as many as 30 or 40 transfusions elsewhere, whose serum contained a high titer of Rh antibodies, but who denied any symptoms of reaction. Surely many of them must have hemolyzed some of the transfused blood asymptomatically, just as did the patient in the case reported.

It is not surprising that such events should rarely be reported, since, in the absence of the characteristic chill, the average clinician does not feel it necessary to search for the less obvious signs of hemolysis. If such search were made, however, it probably would be discovered that, among Rh-negative patients who have received blood previously, apparently uneventful transfusions of Rh-positive blood are not infrequently followed by hemoglobinemia, hemoglobinuria, low-grade icterus and urobilinogenuria, and that such transfusions do not elevate the hemoglobin as they should.

In spite of their apparent innocuousness, such asymptomatic hemolytic reactions must not be dismissed as of no importance. In the first place, transfusions of incompatible blood are at best a waste of blood and of no help to the patient. On that basis alone they should be avoided. Secondly, it has yet to be determined that such reactions do not injure the patient. Only time and thorough study will determine whether there is permanent renal or hepatic damage in such patients. Finally, and most important, there is as yet no way of predicting which patients will hemolyze transfused blood without symptoms and which will die in shock or in renal failure. In view of these facts, it is the opinion of many, including the author, that transfusions of Rh-incompatible blood should be avoided, even in the male patient. The only way in which this can be done is to institute Rh-typing as a routine pre-transfusion procedure and to maintain a source of Rh-negative blood for the Rh-negative patients.

That this is not universally the practice, even with female patients, is due more to a lack of appreciation of its importance by the average physician than to any lack of facilities. Rh-typing techniques have been so simplified that they can be carried out reliably in the smallest laboratories and by the least trained personnel. Reliable Rh antisera are becoming increasingly available and the modern blood banks are prepared to supply Rh-negative blood on call. These facilities will not be properly utilized, however, or extended to smaller communities, where the big city blood bank is not available, until the medical profession becomes more fully aware of the potential for trouble in the Rh-incompatible blood transfusion.

*The technique used was one utilizing the blocking antibody in bovine albumin. The failure to demonstrate Rh-positive cells could not have been due to "blocking" of them by antibodies in the patient's serum.

REFERENCES

1. Diamond, L. K.: Physicochemical and immunological characteristics of Rh antibodies. Read at the International Hematology and Rh Conference, Dallas, Nov. 16, 1946.

2. Diamond, L. K.: Personal communication.

3. Drummond, R., Taylor, G. L., and Edwards, J. T. R.: Potent anti-Rh agglutinins developed in an Rh negative female after multiple transfusions of Rh positive blood, Brit. M. J., 1:584 (April 28), 1945.

4. Hattersley, P. G.: Two popular fallacies regarding Rh, J. Lab. & Clin. Med., 32:423 (April), 1947.

5. Landsteiner, K., and Wiener, A. S.: An agglutinable factor in human blood recognized by immune sera for Rhesus blood, Proc. Soc. Exper. Biol. & Med., 43:223 (Jan.), 1940.

6. Levine, P., and Waller, R. K.: Erythroblastosis in the first born, Blood, 1:143 (March), 1946.

7. Potter, E. L.: Rh—its relation to congenital hemolytic disease and to intragroup transfusion reactions, The Year Book Publishers, Chicago, 1947, pp. 95, 97.

8. Ross, J. B.: Personal communication.

9. Wiener, A. S.: The Rh blood types and some of their applications, Am. J. Clin. Path., 15:106 (March), 1945.

10. Wiener, A. S.: Notes on the pathogenesis of congenital hemolytic disease (erythroblastosis fetalis), Am. J. Clin. Path., 16:319 (May), 1946.

11. Wiener, A. S.: Rh factors in clinical medicine, J. Lab. & Clin. Med., 30:957 (Nov.), 1945.

12. Wiener, A. S., and Sonn-Gordon, E. B.: Simple method of preparing anti-Rh serum in normal male donors, Am. J. Clin. Path., 17:67 (Jan.), 1947.

Head Retraction Reflex

ROBERT WARTENBERG, M.D., *San Francisco*

ON BRISK stretching, every striated muscle reacts with brisk contraction. This reaction constitutes the deep muscle reflex. These reflexes are usually designated in textbooks by such terms as tendon, bone, periosteal, and osteoperiosteal reflexes. These names, however, are misleading, since the tendon, the periosteum, and the bone are simply places on which the blow of the reflex hammer is applied in order to evoke sudden stretching of the muscle. Such stimulation in itself does not initiate the reflex. In elicitation of the reflex, it is solely the stretching of the muscle fibers *en masse* that allows it to come into action. The term "deep muscle reflexes" is, therefore, appropriate. It follows, then, that it is not logical to designate each reflex according to the point of elicitation, since these points may be different and varied. It is far better to apply the names of the involved muscles—which when stretched respond and contract forthwith—than to associate the reflexes with the points of their elicitation, or to give them proper names. Monrad-Krohn in the eighth edition of his popular work, "The Clinical Examination of the Nervous System," uses the terms "glabella reflex (supraorbital periosteal reflex)" and "radialis periosteal reflex (supinator jerk)." How much simpler to say "orbicularis oculi reflex" and "brachioradial reflex"! Why use proper names as Hoffmann, Troemner, Bechterew, when the reflex named for them is, physiologically, a "finger flexor reflex"?

Some muscles react to stretching with contraction more easily than do others. Some are so located that it is difficult to stretch them briskly and effectively, or if they do contract, the contraction and the movement effected thereby is hardly discernible.

It is of paramount importance for the understanding of the deep muscle reflexes and for the evaluation of their manifestations to realize that in some muscles the threshold for contraction on stretching is so high, the visible manifestation of this contraction so delicate, that in normal it is hardly discernible on gross inspection and palpation. This is true, for instance, of the deep muscle reflex of the plantar muscles, the flexors of the toes. The so-called Rossolimo reflex is nothing else than this deep plantar muscle reflex; it is therefore not in itself pathologic, but is only a pathologic exaggeration of a normal but latent deep muscle reflex.

The same applies to the reflex of the muscles in the nape of the neck, which retract the head. This reflex cannot be elicited in normal persons but becomes manifest when the corresponding reflex arc is released from pyramidal control, as in cases of bilateral supracervical affection of the pyramidal tract. To elicit a stretch reflex of these muscles, the patient must keep his neck muscles loose and his head slightly bent forward. The examiner applies a blow downward to the middle of the upper lip in order to effect a brisk bending of the head. When this reflex is positive, the patient answers with a quick retraction of his head. The deep muscles in the nape of the neck, the head retractors, react to sudden stretching in the same way as any other muscles. This is the head retractors' reflex, or, for the sake of euphony, head retraction reflex. This reflex has been found positive in the presence of lesions of the pyramidal tracts above the cervical cords—in diffuse brain lesions, as cerebral arteriosclerosis, hypertensive encephalopathy, cerebral lues. It is further positive in the presence of all spinal lesions which have a tendency to creep upward and to affect the pyramidal tracts of the cerebral hemispheres, for instance in amyotrophic lateral sclerosis, lateral sclerosis, dorsolateral sclerosis. This reflex may thus indicate whether a spinal lesion has transgressed the boundaries of the spinal cord and has affected the pyramidal tracts above the cervical cord.

Physiologically the head retraction reflex belongs to the syndrome of decerebrate rigidity in which the retraction of the head may be very pronounced. It is an expression of the mildest, subclinical form of such decerebrate rigidity.

Read before the Section on Neuropsychiatry at the 77th Annual Session of the California Medical Association, San Francisco, April 11-14, 1948.

University of California Hospital, The Medical Center.